

INTERNATIONAL COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 April 2000 (28.04.00)	Applicant's or agent's file reference AJB/P32147
International application No. PCT/EP99/07003	Priority date (day/month/year) 18 September 1998 (18.09.98)
International filing date (day/month/year) 15 September 1999 (15.09.99)	
Applicant HAYES, Jerome, Francis et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
29 March 2000 (29.03.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer C. Villet</p> <p>Telephone No.: (41-22) 338.83.38</p>
------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------

WHAT IS CLAIMED IS :

1. 7-(3-Aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate.

2. 7-(3-Aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate. $\cdot nH_2O$, wherein n is in the range of from 1 to 4.

3. A compound according to claim 2 wherein n is 1.5.

4. A compound according to claim 2 having peaks at $2\theta = 8.0, 12.2$ and 14.7° in its X-ray diffraction pattern.

5. A compound according to claim 2 having an X-ray diffraction pattern substantially as shown in Figure 7.

6. A compound according to claim 2 wherein n is 3.

7. A compound according to claim 2 having peaks at $2\theta = 7.7$ and 11.8° in its X-ray diffraction pattern.

8. A compound according to claim 2 having an X-ray diffraction pattern substantially as shown in Figure 6.

9. A compound according to claim 2 which has a moisture content of from 4 to 6%.

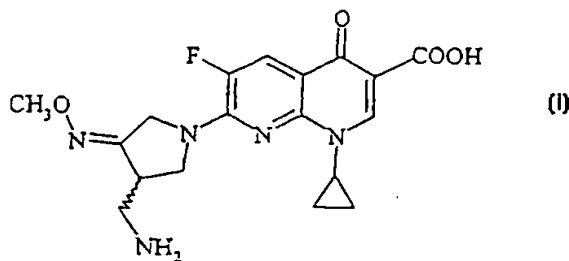
10. A compound according to claim 2 which has a moisture content



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 471/04	A1	(11) International Publication Number: WO 00/17199 (43) International Publication Date: 30 March 2000 (30.03.00)
(21) International Application Number: PCT/EP99/07003 (22) International Filing Date: 15 September 1999 (15.09.99) (30) Priority Data: 9820405.0 18 September 1998 (18.09.98) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HAYES, Jerome, Francis [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). WALSGROVE, Timothy, Charles [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). WELLS, Andrew, Stephen [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). (74) Agent: BLAKEY, Alison, Jane; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE (METHANESULFONATE SESQUIHYDRATE)

**(57) Abstract**

The present invention relates to an improved process for the production of the methanesulfonate sesquihydrate which comprises direct salt and hydrate formation. According to the invention there is provided a process for the production of 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises reacting 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of formula (I) having antibacterial activity and methanesulfonic acid in a solvent comprising at least one water miscible cosolvent and water, and isolating the resulting solid product.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07003

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 688 772 A (LG CHEMICAL LIMITED) 27 December 1995 (1995-12-27) cited in the application * see page 9, line 29-36 * the whole document	1-10
Y	WO 96 39406 A (HANDANYAN LYNNE A ; JOHNSON PHILLIP J (US); MORRIS THOMAS A (US); N) 12 December 1996 (1996-12-12) * see page 1, formula 1, and page 4, preparation A * the whole document	1-10
Y	WO 91 02526 A (PFIZER) 7 March 1991 (1991-03-07) the whole document	1-10

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

31 January 2000

Date of mailing of the international search report

01/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07003

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 805 156 A (KYORIN SEIYAKU KK) 5 November 1997 (1997-11-05) the whole document ---	1-10
Y	EP 0 058 614 A (BELLON LABOR SA ROGER ;DAINIPPON PHARMACEUTICAL CO (JP)) 25 August 1982 (1982-08-25) the whole document ---	1-10
Y	WO 97 36874 A (SMITHKLINE BEECHAM CORP ;DUDDU SARMA (US); PALEPU NAGESWARA R (US)) 9 October 1997 (1997-10-09) the whole document ---	1-10
Y	WO 97 07098 A (PFIZER ;ANDINO MARTA M (US); SINAY TERRY G (US); FIESE EUGENE F (U) 27 February 1997 (1997-02-27) the whole document ---	1-10
Y	PATENT ABSTRACTS OF JAPAN vol. 015, no. 202 (C-0834), 23 May 1991 (1991-05-23) & JP 03 056479 A (TAKESHI YOKOTA), 12 March 1991 (1991-03-12) abstract ---	1-10
P,X	WO 98 42705 A (CHOI HOON ;KIM AE RI (KR); LEE JIN HWA (KR); LEE TAE HEE (KR); NAM) 1 October 1998 (1998-10-01) cited in the application the whole document ---	1-10
E	WO 99 61420 A (UPJOHN CO ;RUNGE THOMAS A (US)) 2 December 1999 (1999-12-02) the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0688772 A	27-12-1995	KR 131999 B	17-04-1998
		CA 2151890 A,C	17-12-1995
		CN 1114959 A	17-01-1996
		DE 69509442 D	10-06-1999
		DE 69509442 T	02-09-1999
		JP 2742248 B	22-04-1998
		JP 8041050 A	13-02-1996
		US 5869670 A	09-02-1999
		US 5962468 A	05-10-1999
		US 5633262 A	27-05-1997
		US 5698570 A	16-12-1997
		US 5840916 A	24-11-1998
		US 5776944 A	07-07-1998
WO 9639406 A	12-12-1996	CA 2223404 A	12-12-1996
		HU 9601540 A	28-02-1997
		AU 703634 B	25-03-1999
		AU 5474996 A	19-12-1996
		BG 100639 A	28-02-1997
		BR 9602630 A	08-09-1996
		CN 1148596 A	30-04-1997
		CZ 9601625 A	16-09-1998
		DE 69503066 D	23-07-1998
		DE 69503066 T	15-10-1998
		EP 0789697 A	20-08-1997
		ES 2117426 T	01-08-1998
		FI 974441 A	05-12-1997
		HR 960267 A	31-08-1997
		IL 118488 A	26-01-1999
		JP 10506650 T	30-06-1998
		LV 11619 A	20-12-1996
		LV 11619 B	20-04-1997
		NO 962321 A	09-12-1996
		NZ 286735 A	26-01-1998
		PL 314604 A	09-12-1996
		SG 54339 A	16-11-1998
		SI 9600185 A	30-04-1997
		SK 71996 A	05-03-1997
		US 5763454 A	09-06-1998
WO 9102526 A	07-03-1991	AT 124040 T	15-07-1995
		AU 623801 B	21-05-1992
		AU 6104290 A	21-02-1991
		CA 2023217 A,C	17-02-1991
		CA 2127561 A	17-02-1991
		CN 1049501 A,B	27-02-1991
		CZ 9004027 A	17-04-1996
		CY 1969 A	05-09-1997
		DD 298399 A	20-02-1992
		DE 69020262 D	27-07-1995
		DE 69020262 T	26-10-1995
		DK 413455 T	14-08-1995
		EG 19251 A	29-09-1994
		EP 0413455 A	20-02-1991
		ES 2074131 T	01-09-1995
		FI 964520 A	11-11-1996
		GR 3017072 T	30-11-1995
		HK 1000207 A	06-02-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9102526 A		IE 66202 B	13-12-1995
		IL 95331 A	31-07-1995
		JP 7149758 A	13-06-1995
		JP 8019099 B	28-02-1996
		JP 1975517 C	27-09-1995
		JP 3086875 A	11-04-1991
		JP 7002734 B	18-01-1995
		KR 9304844 B	09-06-1993
		LU 90310 A	25-01-1999
		LU 90311 A	25-01-1999
		NO 300214 B	28-04-1997
		NZ 234920 A	25-06-1992
		PL 166381 B	31-05-1995
		PT 94998 A, B	18-04-1991
		RU 2049777 C	10-12-1995
		US 5266569 A	30-11-1993
		US 5164402 A	17-11-1992
		US 5229396 A	20-07-1993
EP 0805156 A	05-11-1997	JP 8176143 A	09-07-1996
		AU 694946 B	06-08-1998
		AU 3994695 A	10-07-1996
		US 5880283 A	09-03-1999
		CA 2208704 A	27-06-1996
		CN 1171108 A	21-01-1998
		HU 77945 A	28-12-1998
		WO 9619472 A	27-06-1996
EP 0058614 A	25-08-1982	JP 1618494 C	12-09-1991
		JP 2043753 B	01-10-1990
		JP 57134482 A	19-08-1982
		AU 547082 B	03-10-1985
		AU 8017382 A	19-08-1982
		CA 1216292 A	06-01-1987
		CS 8200998 A	16-07-1987
		DD 202573 A	21-09-1983
		DK 63482 A, B,	14-08-1982
		ES 509538 A	01-08-1983
		FI 820466 A, B,	14-08-1982
		KR 8700322 B	27-02-1987
		MX 158194 A	16-01-1989
		NO 820430 A, B,	16-08-1982
		PH 18177 A	12-04-1985
		PL 235049 A	27-09-1982
		US 4442101 A	10-04-1984
		YU 26582 A	30-04-1986
		ZA 8200740 A	29-12-1982
WO 9736874 A	09-10-1997	AU 2547097 A	22-10-1997
		BR 9708336 A	03-08-1999
		CN 1214682 A	21-04-1999
		CZ 9803101 A	17-03-1999
		EP 0889880 A	13-01-1999
		NO 984503 A	28-09-1998
		NZ 332008 A	28-05-1999
		PL 329046 A	01-03-1999
		SK 132298 A	10-03-1999

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 99/07003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9707098 A	27-02-1997	AU 710984 B AU 5908496 A BG 102289 A BR 9610766 A CA 2228752 A CN 1198739 A CZ 9800390 A EP 0843661 A HR 960372 A HU 9802862 A JP 10510552 T NO 980574 A NZ 309134 A PL 325050 A	07-10-1999 12-03-1997 30-09-1998 13-07-1999 27-02-1997 11-11-1998 17-02-1999 27-05-1998 30-04-1998 28-04-1999 13-10-1998 10-02-1998 29-09-1999 06-07-1998
JP 03056479 A	12-03-1991	NONE	
WO 9842705 A	01-10-1998	AU 6636698 A NO 994595 A	20-10-1998 21-09-1999
WO 9961420 A	02-12-1999	NONE	

PCT

REC'D 22 DEC 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AJB/P32147	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/07003	International filing date (day/month/year) 15/09/1999	Priority date (day/month/year) 18/09/1998
International Patent Classification (IPC) or national classification and IPC C07D471/04		
Applicant SMITHKLINE BEECHAM P.L.C. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 29/03/2000	Date of completion of this report 20.12.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stellmach, J Telephone No. +49 89 2399 8279



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07003

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-4 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07003

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION V -----

1. Prior art

Documents (1) - (10), which were cited in the **International Search Report** and the **Written Opinion** are considered to represent relevant prior art in this **Preliminary Examination Report**; the numbering will be adhered to in the rest of the procedure.

- (1) EP-A-0 688 772
- (2) WO-A-96/39 406
- (3) WO-A-91/02526
- (4) EP-A-0 805 156
- (5) EP-A-0 058 614
- (6) JP-A-3,056,479
- (7) WO-A-97/36 874
- (8) WO-A-97/07 098
- (9) WO-A-98/42 705
- (10) WO-A-99/61 420

2. Novelty

2.1 Documents (9) and (10) are only relevant for the purposes of **Rules 33.1 c, 64.3 and 70.10 PCT** (see also part VI, certain documents) and are thus not taken into account for the **Preliminary Examination Report**. If the priority date is not valid for the complete subject-matter, documents (9) and (10) may become relevant prior art in a possible regional / national phase.

2.2 The process of claim 1 refers to the production of a specific **naphthyridine** carboxylic acid methane sulfonate sesquihydrate by reacting the carboxylic acid with

methane-sulphonic acid and water together with a cosolvent. In citation (1) the synthesis of the **carboxylic acid** is described. On page 9, line 33-36, the preparation of the methane-sulphonic acid salt (acid addition salt) is suggested. Citations (2) - (6) describe the preparation of **methane sulfonate** and **sesquihydrates** of various **Naphthyridines** and **quinolones**. Citations (7) and (8) describe the preparation of **methane sulfonate** di- and tri-hydrates of structurally remote pharmaceutically active compounds. Since none of the cited prior art documents describes the preparation of the specific compound of the claimed process, the requirements of **Article 33 (2) PCT** are met for claim 1 and its dependant claims 2- 10.

3. Inventive step

3.1 For the assessment of inventive step (**Article 33 (3) PCT**) of the claimed subject-matter, a document has to be identified which represents the closest prior art for the claimed process. Starting from the document (1), the first technical problem underlying the application in suit (**Article 33 (3) PCT, Rule 5.1 (a) (iii) PCT**) can be considered to be the provision of a process for the production of the specific naphthyridine carboxylic acid methane sulfonate sesquihydrate of present claims 1-10. This problem is solved by reacting the carboxylic acid with methane sulphonic acid and water together with a cosolvent.

3.2 The reaction is in general known from (1) - (6). It is known from citation (2) that e.g. the methane sulfonate monohydrate of a **naphthyridine carboxylic acid** is formed by reacting the **carboxylic acid** with **methane sulphonic acid** in a mixture of a water and a cosolvent. Claim 1 is thus to be considered as a **process of analogy**. Accordingly, the skilled man would regard the choice of the specific **naphthyridine** compound according to the similar process in the prior art to be useful in order to yield the **methane sulfonate sesquihydrate**. All what is needed is a basic understanding of the principles of Organic chemistry.

3.3 **Analogous processes** yielding known products are only inventive if a surprising effect is made credible in comparison with the closest prior art e.g. if the yield of the process or the quality of the product were better. The notional skilled person was provided with a **clear** hint from the prior art pointing him in the direction of the claimed process, and it was only necessary to confirm experimentally that the highly probable result was in fact obtained. The necessity of experimental confirming a reasonably expected result (in the present case which specific hydrate was actually yielded by the respective analysis) does not render an invention unobvious. The features described

above are merely ones of several possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill in order to solve the problem posed. The skilled man having knowledge of the teaching of documents (1) - (8) with a reasonable expectation of success would expect that the process as claimed in claim 1 would yield methane sulfonate hydrate having a basic understanding of elementary Organic Chemistry. No positive contribution to **inventive step** can be seen in solving this particular problem, because the skilled man would expect the claimed process to be suitable for his purpose i.e. without the exercise of inventive skill in order to solve the problem posed. The Applicant's attention is furthermore drawn to the fact that the Examining Division must satisfy itself that the problem is actually solved. Moreover, it is common practice that the modifying feature should not only characterize the invention in the claim, i.e. distinguish it from the prior art, but must contribute causally to the improvement of the capability thereby achieved. Given the claimed process to be expected to yield the product, an inventive step could only be recognized if the Applicant could demonstrate that the presently claimed process illustrates actually surprising effects in comparison with the closest prior art i.e. only if the solution of the problem underlying the present application is an process - a process which has unforeseeable advantages over the prior art, an inventive step in the sense of **Article 33 (3) PCT** could be recognized.

3.4 The Applicant in his letter dated 21.9.00 has argued that citation (1) does not refer to hydrated forms of the claimed quinoline carboxylic acids. It is respectfully submitted that formula (I) of claim 1 refers to any solvate of the compounds and it is common general knowledge that hydrates are specific solvates. Moreover, the argumentation that the fact that in the analogous processes of documents 7 and 8 dihydrates and trihydrates were produced would render the claimed process inventive is not convincing. As already outlined in the Written Opinion all what the skilled person has to do is to verify which hydrate is actually formed when the chemical process was performed and this is confirmed by the Applicant's statement. Also the reference to document (9), in ex. 3 of which **methane sulfonate sesquihydrate** is produced in a similar process, does not render the claimed process inventive. The statement that the product, the **methane sulfonate sesquihydrate** is novel and inventive is not substantiated. On the contrary, in test example 5 it is stated that the sesquihydrate has the same chemical stability as the anhydrate. Moreover, it is for consideration whether at least claim 1 of the application in suit is novel in a possible national phase. a proof for the improved solubility and constant moisture content appears to be missing.

3.5 Finally, it is realized that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. Furthermore, the extent of a "reasonable generalisation" only depends upon the question of the relative distance to the prior art compounds. It is stressed that only such variants of the processes can be claimed which are a solution to the above stated problem i.e. which illustrate the alleged unexpected effects.

4. Industrial applicability

No objection re industrial applicability of claims 1 - 10 arises insofar the claimed process would illustrate unexpected effects (**Article 33 (4) PCT**).

SECTION VII -----

1. Since the documents (2) - (8) and (10) were not identified in the description and the relevant background art disclosed therein was not be briefly discussed, the requirements of **Rule 5.1 (a) (ii) PCT** are not met..
2. Depending upon the actual technical problem which is solved by the application, to meet the requirements of **Rule 6.3 (b) PCT** the independent process claim 1 should be properly cast in the two part form, with those features which in combination are part of the prior art.

SECTION VIII-----

The Applicant is informed that the breadth of the claims has to be such that it comprises only variants which are able to solve the problem underlying the alleged invention being a prerequisite for the acknowledgement of inventive step (**Article 33 (3) PCT**).

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AJB/P32147	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/07003	International filing date (day/month/year) 15/09/1999	(Earliest) Priority Date (day/month/year) 18/09/1998
Applicant SMITHKLINE-BEECHAM P.L.C. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE
(METHANESULFONATE SESQUIHYDRATE)**

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

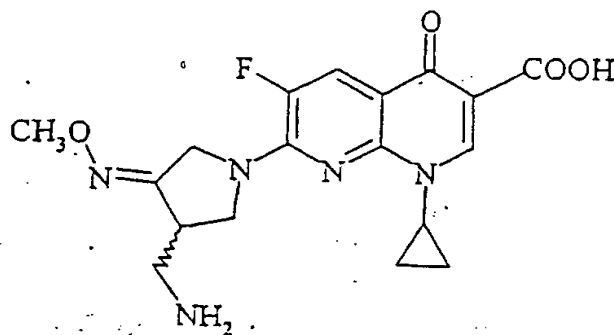
☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates to an improved process for the production of the methanesulfonate sesquihydrate which comprises direct salt and hydrate formation. According to the invention there is provided a process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises reacting 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of formula I having antibacterial activity



I

and methanesulfonic acid in a solvent comprising at least one water miscible cosolvent and water, and isolating the resulting solid product.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07003

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 688 772 A (LG CHEMICAL LIMITED) 27 December 1995 (1995-12-27) cited in the application * see page 9, line 29-36 * the whole document	1-10
Y	WO 96 39406 A (HANDANYAN LYNNE A ; JOHNSON PHILLIP J (US); MORRIS THOMAS A (US); N) 12 December 1996 (1996-12-12) * see page 1, formula 1, and page 4, preparation A * the whole document	1-10
Y	WO 91 02526 A (PFIZER) 7 March 1991 (1991-03-07) the whole document	1-10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

31 January 2000

Date of mailing of the international search report

01/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07003

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 805 156 A (KYORIN SEIYAKU KK) 5 November 1997 (1997-11-05) the whole document ----	1-10
Y	EP 0 058 614 A (BELLON LABOR SA ROGER ;DAINIPPON PHARMACEUTICAL CO (JP)) 25 August 1982 (1982-08-25) the whole document ----	1-10
Y	WO 97 36874 A (SMITHKLINE BEECHAM CORP ;DUDDU SARMA (US); PALEPU NAGESWARA R (US)) 9 October 1997 (1997-10-09) the whole document ----	1-10
Y	WO 97 07098 A (PFIZER ;ANDINO MARTA M (US); SINAY TERRY G (US); FIESE EUGENE F (U) 27 February 1997 (1997-02-27) the whole document ----	1-10
Y	PATENT ABSTRACTS OF JAPAN vol. 015, no. 202 (C-0834), 23 May 1991 (1991-05-23) & JP 03 056479 A (TAKESHI YOKOTA), 12 March 1991 (1991-03-12). abstract ----	1-10
P,X	WO 98 42705 A (CHOI HOON ;KIM AE RI (KR); LEE JIN HWA (KR); LEE TAE HEE (KR); NAM 1 October 1998 (1998-10-01) cited in the application the whole document ----	1-10
E	WO 99 61420 A (UPJOHN CO.; RUNGE THOMAS A (US)) 2 December 1999 (1999-12-02) the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07003

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0688772	A	27-12-1995	KR 131999 B	17-04-1998
			CA 2151890 A,C	17-12-1995
			CN 1114959 A	17-01-1996
			DE 69509442 D	10-06-1999
			DE 69509442 T	02-09-1999
			JP 2742248 B	22-04-1998
			JP 8041050 A	13-02-1996
			US 5869670 A	09-02-1999
			US 5962468 A	05-10-1999
			US 5633262 A	27-05-1997
			US 5698570 A	16-12-1997
			US 5840916 A	24-11-1998
			US 5776944 A	07-07-1998
<hr/>				
WO 9639406	A	12-12-1996	CA 2223404 A	12-12-1996
			HU 9601540 A	28-02-1997
			AU 703634 B	25-03-1999
			AU 5474996 A	19-12-1996
			BG 100639 A	28-02-1997
			BR 9602630 A	08-09-1996
			CN 1148596 A	30-04-1997
			CZ 9601625 A	16-09-1998
			DE 69503066 D	23-07-1998
			DE 69503066 T	15-10-1998
			EP 0789697 A	20-08-1997
			ES 2117426 T	01-08-1998
			FI 974441 A	05-12-1997
			HR 960267 A	31-08-1997
			IL 118488 A	26-01-1999
			JP 10506650 T	30-06-1998
			LV 11619 A	20-12-1996
			LV 11619 B	20-04-1997
			NO 962321 A	09-12-1996
			NZ 286735 A	26-01-1998
			PL 314604 A	09-12-1996
			SG 54339 A	16-11-1998
			SI 9600185 A	30-04-1997
			SK 71996 A	05-03-1997
			US 5763454 A	09-06-1998
<hr/>				
WO 9102526	A	07-03-1991	AT 124040 T	15-07-1995
			AU 623801 B	21-05-1992
			AU 6104290 A	21-02-1991
			CA 2023217 A,C	17-02-1991
			CA 2127561 A	17-02-1991
			CN 1049501 A,B	27-02-1991
			CZ 9004027 A	17-04-1996
			CY 1969 A	05-09-1997
			DD 298399 A	20-02-1992
			DE 69020262 D	27-07-1995
			DE 69020262 T	26-10-1995
			DK 413455 T	14-08-1995
			EG 19251 A	29-09-1994
			EP 0413455 A	20-02-1991
			ES 2074131 T	01-09-1995
			FI 964520 A	11-11-1996
			GR 3017072 T	30-11-1995
			HK 1000207 A	06-02-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9102526 A		IE 66202 B	13-12-1995
		IL 95331 A	31-07-1995
		JP 7149758 A	13-06-1995
		JP 8019099 B	28-02-1996
		JP 1975517 C	27-09-1995
		JP 3086875 A	11-04-1991
		JP 7002734 B	18-01-1995
		KR 9304844 B	09-06-1993
		LU 90310 A	25-01-1999
		LU 90311 A	25-01-1999
		NO 300214 B	28-04-1997
		NZ 234920 A	25-06-1992
		PL 166381 B	31-05-1995
		PT 94998 A, B	18-04-1991
		RU 2049777 C	10-12-1995
		US 5266569 A	30-11-1993
		US 5164402 A	17-11-1992
		US 5229396 A	20-07-1993
EP 0805156 A	05-11-1997	JP 8176143 A	09-07-1996
		AU 694946 B	06-08-1998
		AU 3994695 A	10-07-1996
		US 5880283 A	09-03-1999
		CA 2208704 A	27-06-1996
		CN 1171108 A	21-01-1998
		HU 77945 A	28-12-1998
		WO 9619472 A	27-06-1996
EP 0058614 A	25-08-1982	JP 1618494 C	12-09-1991
		JP 2043753 B	01-10-1990
		JP 57134482 A	19-08-1982
		AU 547082 B	03-10-1985
		AU 8017382 A	19-08-1982
		CA 1216292 A	06-01-1987
		CS 8200998 A	16-07-1987
		DD 202573 A	21-09-1983
		DK 63482 A, B	14-08-1982
		ES 509538 A	01-08-1983
		FI 820466 A, B	14-08-1982
		KR 8700322 B	27-02-1987
		MX 158194 A	16-01-1989
		NO 820430 A, B	16-08-1982
		PH 18177 A	12-04-1985
		PL 235049 A	27-09-1982
		US 4442101 A	10-04-1984
		YU 26582 A	30-04-1986
		ZA 8200740 A	29-12-1982
WO 9736874 A	09-10-1997	AU 2547097 A	22-10-1997
		BR 9708336 A	03-08-1999
		CN 1214682 A	21-04-1999
		CZ 9803101 A	17-03-1999
		EP 0889880 A	13-01-1999
		NO 984503 A	28-09-1998
		NZ 332008 A	28-05-1999
		PL 329046 A	01-03-1999
		SK 132298 A	10-03-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07003

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9707098	A	27-02-1997	AU 710984 B	07-10-1999
			AU 5908496 A	12-03-1997
			BG 102289 A	30-09-1998
			BR 9610766 A	13-07-1999
			CA 2228752 A	27-02-1997
			CN 1198739 A	11-11-1998
			CZ 9800390 A	17-02-1999
			EP 0843661 A	27-05-1998
			HR 960372 A	30-04-1998
			HU 9802862 A	28-04-1999
			JP 10510552 T	13-10-1998
			NO 980574 A	10-02-1998
			NZ 309134 A	29-09-1999
			PL 325050 A	06-07-1998
JP 03056479	A	12-03-1991	NONE	
WO 9842705	A	01-10-1998	AU 6636698 A	20-10-1998
			NO 994595 A	21-09-1999
WO 9961420	A	02-12-1999	NONE	